COMPUTATIONAL ANALYSIS OF CHALCONE DERIVATIVES AS POTENTIAL ANTIMICROBIAL AGENTS

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DECLARATION

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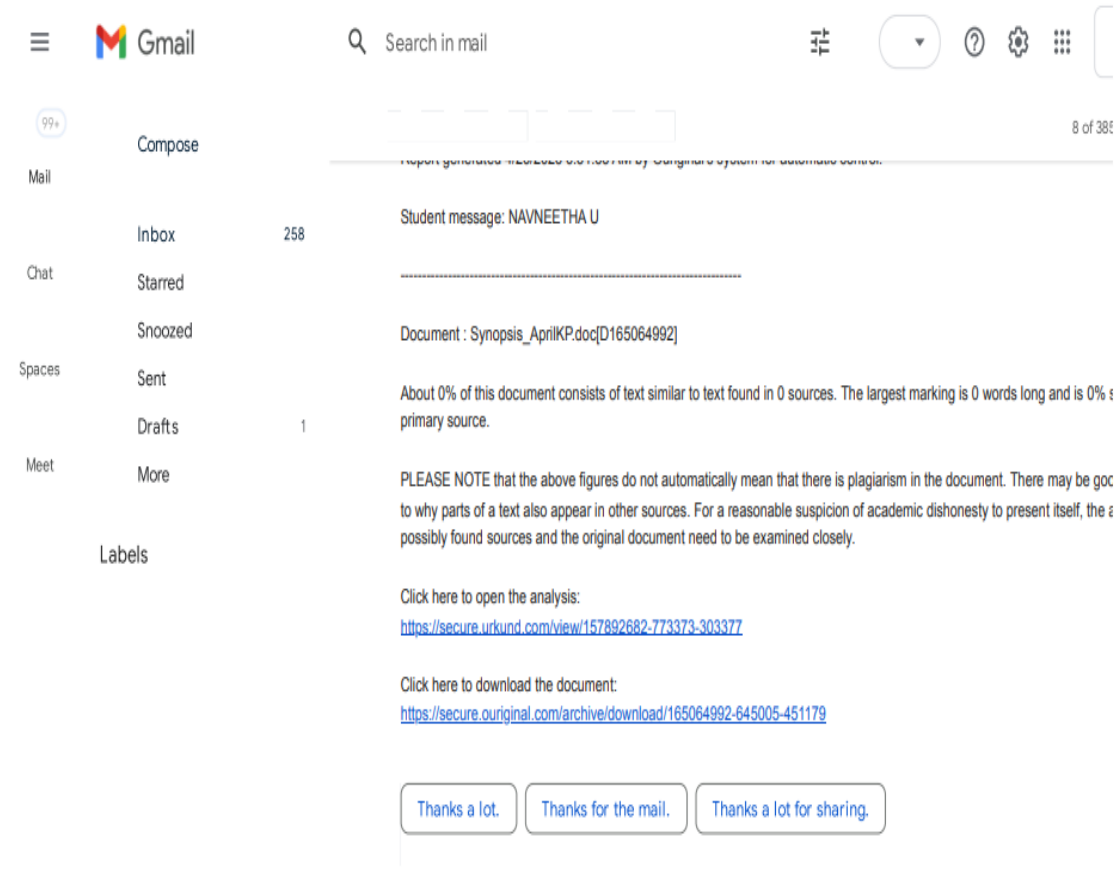
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1. TITLE:

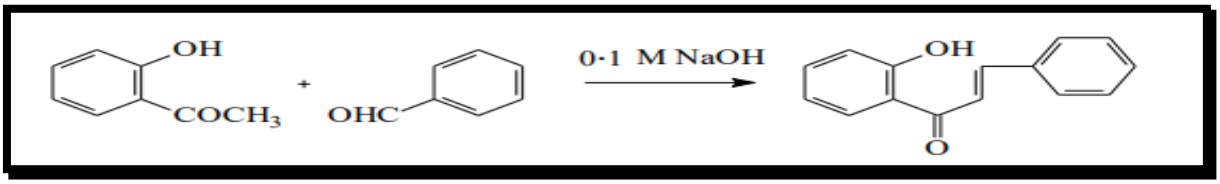
"COMPUTATIONAL ANALYSIS OF CHALCONE DERIVATIVES AS POTENTIAL ANTIMICROBIAL AGENTS"

2.INTRODUCTION:

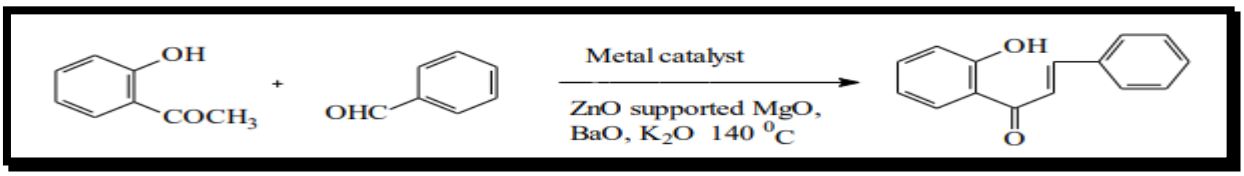
One of the most significant types of organic chemicals found in nature or produced in the lab are heterocyclic systems. These substances can be used to treat frequently occurring disorders because of their wide range of biological activity. Chalcones are polyphenolic compounds with aromatic ketone and enone origins in plants. They are open-chain flavonoids chemically speaking, with a three carbon, -unsaturated carbonyl system connecting the two aromatic rings. Chalcones are widely distributed in nature, from ferns to higher plants, and many of them have aryl rings that have undergone polyhydroxylation. The name Chalcones was proposed by **Kostanecki** and **Tambour. [1]**

2.1. General Methods of Synthesis of Chalcones:

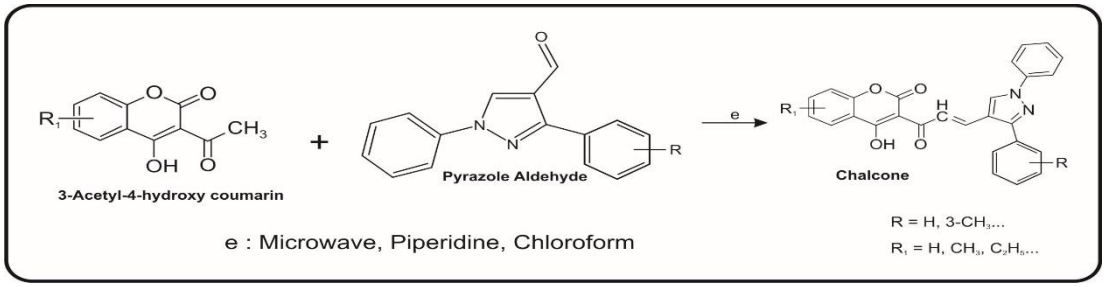
- Acetophenones and aromatic aldehydes can be combined to form Chalcones by an aldol condensation reaction that is catalysed by an acid or base. In the presence of 0.1 M NaOH, benzaldehyde and 2'-hydroxyacetophenone combine to produce Chalcone. [2]



- Liquid phase Claisen–Schmidt condensation between 2' - hydroxyacetophenone and benzaldehyde was carried out over a zinc oxide supported metal oxide catalyst under solvent free conditions to form 2' - hydroxyChalcone [3]

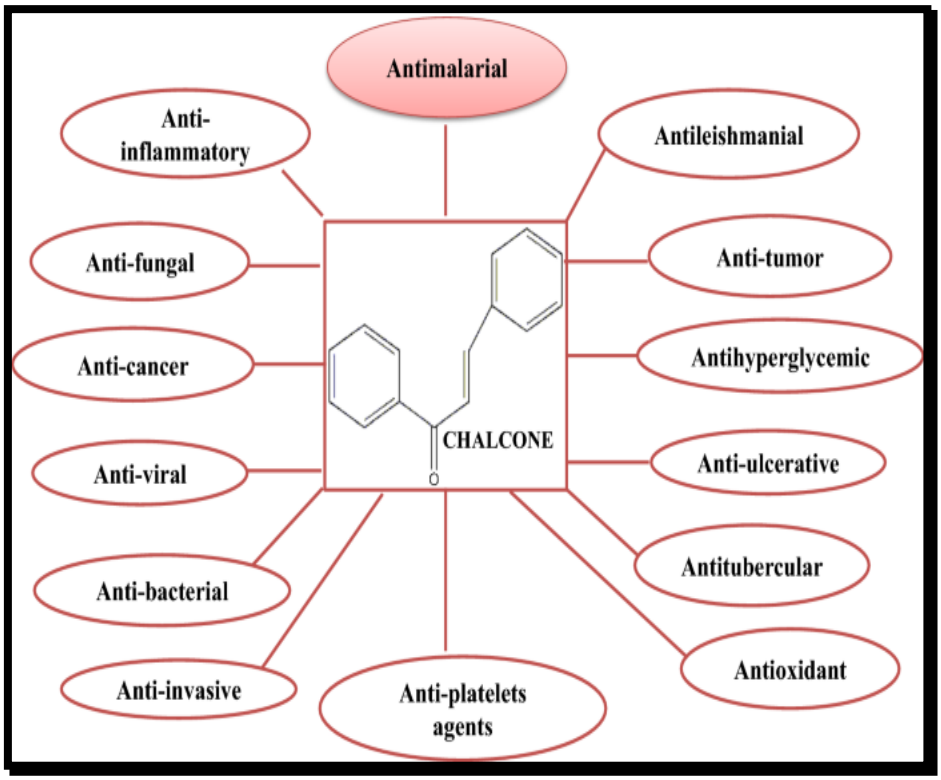


- Microwave synthesis between 3-Acetyl-4 - hydroxy coumarin and pyrazole aldehyde was carried out over piperidine, chloroform to form Chalcone [4]



2.2 Pharmacological activities exhibited by Chalcones:

a. Antimalarial
b. Anti inflammatory
c. Antifungal
d. Anticancer
e. Antiviral
f. Antibacterial
g. Anti platelets
h. Antioxidant
i. Antitumor
j. Antitubercular
k. Antiulcerative
l. Antihyperglycemic.



2.3. Therapeutic Potential of Chalcones:

Chalcone is a distinctive template with a number of biological functions and is a well-known intermediary in the synthesis of numerous heterocyclic compounds [5]. They are terrigenous plants' secondary metabolites and the building blocks for the manufacture of flavonoids. These unsaturated ketones are made to have more biological activity by introducing a halogen into the benzenoid portion of the compound [6].

A variety of biological and pharmacological activities, including antimicrobial, anti-inflammatory, analgesic, cytotoxic, antitumor, anti-malarial, anti-HIV, anti-ulcerative, anti-leishmanial, antioxidant, antiprotozoal, antihistaminic, antifeedant, immunomodulatory, anticonvulsant, antihyperglycemic, antihyperlipidemic, and antiplatelet activities have been reported for compounds with [7].

The antibacterial action of Chalcones is determined to be caused by the presence of a reactive, unsaturated keto function, which may change depending on the kind of substituent and where it is located on the aromatic rings. Chalcones thus continue to garner a lot of scientific interest due to their connections to numerous biological processes. It is becoming more widely known that Chalcones have antibacterial properties. According to the type and location of the substituents on the aromatic rings, the presence of a reactive, unsaturated keto function in Chalcones underwent conjugate addition with a nucleophilic group, such as a thiol group in a necessary protein, and this may have contributed to or altered their antimicrobial activity [8].

2.4 Computer-aided drug design:

The process of drug discovery and development is very expensive and time consuming process. Traditional approaches of discovering drug rely on a step-wise synthesis and screening of large number of compounds to identify a potential candidate.

Over the past ten to twenty years, there is an increased effort to apply computational techniques to the combined chemical and biological space in order to streamline drug discovery, design, development and optimization. [9]

Computational methods are expected to play an imperative role in understanding the specific molecular recognition events of the target macromolecule with candidate hits leading to the design of improved leads for the target [10]

Computer Aided Drug Design (in silico) approaches have been widely employed in Lead Identification and Lead Optimization stages of drug development against various targets over the years. In comparison to traditional drug discovery methods rational drug design methods bring down the time and cost involved in drug development process. Advances in computational techniques and hardware have facilitated the application of in silico methods in the discovery process.

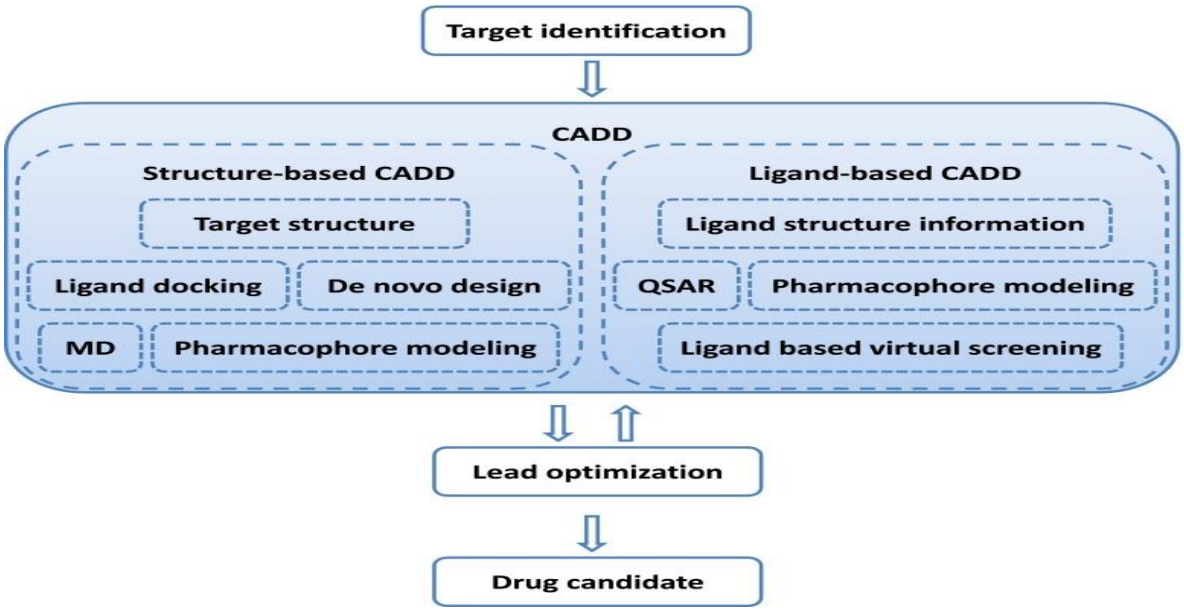
Computer aided techniques has improved the drug discovery and development process and minimise the expenses and failures. [11-15]

2.5. Types of Drug Design:

Drug designing approaches can be broadly classified in two categories: ligand-based drug design and structure-based drug design.

Structure-Based: Direct drug design also known as structure based drug design is dependent on the three-dimensional structure of the biological target. This can be obtained by the use of techniques like x-ray crystallography or NMR spectroscopy. The availability of the therapeutic target proteins' three-dimensional structures into the binding site cavity form the basis of structure-based drug design. [16-18].

Ligand-Based: The indirect drug design, commonly referred to as ligand-based drug design, is based on fact that several compounds bind to the desired biological target. With the help of these extra molecules, a pharmacophore model that details the essential structural conditions for a molecule to bind to the target can be created. Ligand-based drug design, is used when the target receptor's three-dimensional structure is unavailable. [19]



2.6. Importance of using Computational methods are as follows:

- Computational approaches can replace traditional experimentation, which uses animal and human models, saving time and money.

- Decreases the likelihood of drug resistance, which would stimulate the production of lead compounds that would specifically address the underlying cause.
- The development of excellent datasets and libraries that can be enhanced for high molecular diversity or similarity is another benefit of computational approaches.

2.7. Quantitative Structure Activity Relationship:

Quantitative Structure Activity Relationship (QSAR) is one of the widely used approaches in ligand based drug designing processes.

Quantitative Structure Activity Relationship (QSAR) paradigm is based on the assumption that there is an underlying relationship between the molecular structure and biological activity. On the basis of this assumption QSAR study establish a correlation between various molecular properties of a series of molecular compound with their well-known biological activity. [20]

QSAR studies have been investigated on the basis of the fact that the biological activity of the compound is a function of its physicochemical properties. [21]

Quantitative Structure Activity Relationships (QSAR) analyses the correlation between the structural features and the biological activity in order to predict the activity level of new compounds. [22]

Quantitative Structure Activity Relationships (QSAR) are empirical statistical models, and are a mature part of the computational chemistry.

The QSAR methodology is based on the concept that the differences observed in the biological activity of a series of compounds can be quantitatively correlated with differences in their molecular structure. As a result, al biological activities and functions of molecules relate to specific molecular descriptors and specific regression techniques can be used to estimate the relative roles of those descriptors contributing to the biological effect. [23-24]

A major goal of Quantitative Structure Activity Relationship (QSAR) studies is to find a mathematical relationship between the activity or property under investigation, and one or more descriptive parameters or descriptors related to the structure of the molecule. [25]

QSAR Development Process:

The first major step in a QSAR study is the entry of the molecular structures and generation of the 3-D models. The 3-D molecular models are needed for geometric descriptor calculations. [26]

The second major step in a QSAR study is the generation of the molecular structure descriptors.

The third step is selection of the most important descriptors by using feature selection methods. [27]

The fourth major step in a QSAR study is the generation of the QSAR models using the descriptor sets. [28]

The fifth and last step is to validate the model by predicting the activity of compounds in the external prediction set. The results obtained by the predictions should be compared to those achieved for the training set and cross validation set to easily understand model’s fitness level. [29]

3.LITERATURE REVIEW:

Literature survey revealed that Chalcones possess a broad spectrum of biological activities like anti-bacterial, anti-fungal, anti -inflammatory and anti- viral activities.

Deepa Gupta, D.K. Jain., (2016) prepared derivatives of Chalcones by Claisen - Schmidt condensation. Ten derivatives were synthesized and were biologically screened for antifungal activity. It explained that among the Chalcone derivative synthesized ,4-chloro derivative showed antifungal activity superior to ketoconazole. [30]

Vyas et al., (2017) gave concept that Chalcones are synthesized by condensation of ketones with aromatic aldehydes in the presence of suitable bases. They are very useful intermediates for the synthesis of five, six and seven-membered heterocyclic, role in the disease and parasite resistance of plants and along with it has a wide range of application for pharmaceutical purposes. [31]

Marcelo N. Gomes. et al., (2018) summarized strategies for the design and synthesis of new Chalcone derivatives and state-of-the-art medicinal chemistry strategies. They have also emphasized on the utilization of computer-assisted drug design approaches to Chalcones and addressed its usefulness in optimizing research outputs which can lead to more successful and cost-effective drug discovery approaches. They have also explored possible solutions to existing limitations of using Chalcones. [32]

Sahu U. et al., (2019) said that Chalcone is an open-chain flavonoid. Its main chain contains two aromatic rings connected by saturated three-carbon α, β carbonyl groups. Chalcone is polyhydroxylated on the aromatic ring, and the phenol group exists in their basic structure, showing free radical quenching properties. Due to their different pharmacological properties, plant extracts rich in Chalcone or Chalcone compounds are also attracting attention as drugs or food preservatives. [33]

Surendra Babu Lagu. et al., (2020) studied the antifungal activity of novel fluorinated compounds of Chalcones having trifluoromethyl and trifluoromethoxy as substituents. Chalcones with trifluoromethoxy groups showed higher antifungal characteristics than those with trifluoromethyl group. [34]

Ibrahim, T. Set al., (2021) examined how Chalcone derivatives affected inflammation. The inhibitory activity of two series of synthesised Chalcone/aryl carboximidamides hybrids against iNOS and PGE2 was assessed. According to the findings, Chalcone/aryl carboximidamides in particular could be employed as attractive lead candidates for strong anti-inflammatory drugs. [35]

Arun Bahadur Gurung et al., (2021) highlighted the two important categories of computer-aided drug design, viz., the ligand-based as well as structured-based drug discovery. Various computational techniques Molecular docking and pharmacophore modelling, quantitative structure-activity relationship has emerged as an efficient computational tools of identifying potential lead compounds in drug design process. [36]

Narwal et al. (2021) synthesized a variety of substituted Chalcones and subjected them to antibacterial assay against several bacterial strains, including S. aureus, B. subtilis, E. coli, P. aeruginosa and Salmonella enterica. The authors analyzed several significant characteristics of synthesized Chalcones for their antibacterial action and reported that NO_2, NH_2 and OH appeared to play an essential role in Chalcones antibacterial action. Other than that, electron donating groups such as hydroxyl and methoxy groups at ring B helped to boost the antibacterial activity against B. subtilis and P. aeruginosa. [37]

Gayathri Rajendran et al., (2022) summarize the structures from natural sources, synthesis methods, biological characteristics against infectious and non-infectious diseases, and uses of Chalcones over the past decade, and their structure–activity relationship studies are detailed in depth. The review provides guidelines for the future design and synthesis of various Chalcones. In addition, this could be highly supportive for medicinal chemists to develop more promising candidates for various infectious and non-infectious diseases. [38]

Jagjit Singh Dhaliwal et al., (2022) describe the main characteristics of Chalcone and its derivatives, including their method synthesis and pharmacotherapeutics applications with molecular mechanisms. Changing the structure by adding substituent groups to the aromatic ring can increase potency, reduce toxicity, and broaden pharmacological action. This report also summarized the potential health benefits of Chalcone derivatives, particularly antimicrobial activity. [39]

Aysha Siddiqa et al., (2023) The present study describes the synthesis of new 2-Hydroxy-5-nitro Chalcones the flavonoid family by the condensation of acetophenone and benzaldehydes. Molecular docking analysis revealed that all the compounds had a marked affinity for Keap1 and computational studies revealed that all compounds possessed antioxidant potential. These studies suggest that these new 2-Hydroxy-5-nitro Chalcones are potential anti-oxidant and anti-inflammatory compounds. [40]

4. OBJECTIVE:

1. To study the Antimicrobial Potential of selected Chalcone derivatives using computer-aided drug design technologies.
2. To establish a meaningful correlation between the Biological activities of Chalcone derivatives and their molecular descriptors using QSAR approach.
3. To find out the Chalcone derivatives exhibiting better anti -microbial properties.
4. To design/fabricate the new Chalcone derivatives with enhanced anti -microbial potential.
5. To propose important insights for the creation of novel drugs.

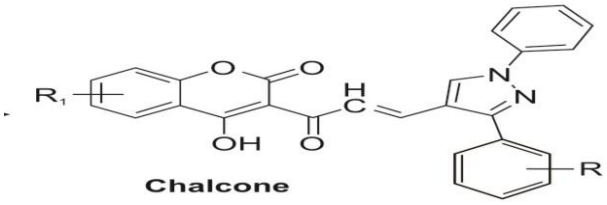
5. RATIONALE:

The preliminary research demonstrates that Chalcones have a straightforward favoured scaffold and are useful lead compounds for drug discovery. There has already been a great deal of work done in the area of computational analysis of Chalcone derivatives, but there is still room to look for even more strong anti-microbial Chalcone derivatives. The goal of the current work is to analyse Chalcone derivatives using a novel combination of structural, length, and breadth descriptors in a Ligand-based drug development technique.
The current effort will also demonstrate how time, labour, and money-efficient QSAR modelling is for finding compounds and lead candidates in the early stages of the drug discovery process.

Ligand-based pharmacophore model generation relies on information regarding the known biological activity of ligands without any structural information for the macromolecular target. The elucidation of a shared feature pharmacophore is based on the 3D alignment of the conformational models from active compounds. A molecular superimposition algorithm arranges the 3D structures of the training compounds in such a way that equal chemical functionalities are located in similar positions. Computational models representing pharmacophores have shown unique potential in scaffold hopping. Therefore, pharmacophore models are frequently applied to generate novel starting points for drug design campaigns [41-43].

6. PROPOSED METHODOLOGY:

Chalcone derivatives will be selected for present study.
Chalcone Derivatives Exhibiting Antimicrobial Property: [44]



$R = H, 3\text{-}CH_3\ldots$
$R_1 = H, CH_3, C_2H_5\ldots$

The employed methodology will be used to predict the antimicrobial activity for the synthesized Chalcones:

Ligand based Drug Design:

Ligand-based Drug Design is based on an understanding of other compounds that bind to the desired biological target.

Quantitative Structural Activity Relationship (QSAR):

QSAR describes the mathematical relationships between the structural attributes and target properties of a set of chemicals.

- The methodology used is two-fold, after doing literature survey, a series of Chalcone Derivatives will be employed for the study of QSAR.
- Combination of Hansch, Verloop and Quantum Parameters will be calculated for all the selected Chalcone derivatives by using the structural details of the compounds.
- Combination of Hansch, Verloop and Quantum Parameters will be calculated for all the selected Chalcone derivatives by using the structural details of the compounds.
- The Hansch, Verloop and Quantum Parameters will act as independent variables and antimicrobial activities as dependent variables, to model the relationship between molecular descriptors and biological activity of Chalcone derivatives by using DATA Analysis, ORIGIN, Regress-1 software.
- Stepwise Regression method will be used to derive the most significant model as a calibration model, which then be used in drug-designing.
- The validation and predictive capabilities of the QSAR model will be assessed using a range of statistical techniques.
- After getting the prominent outcomes from QSAR modeling, ADMET and Molecular docking studies will be analyzed using vivid software *viz* Swiss ADME, AUTODOCK, Molegro.

Biological Activity &Parameters Used in Present Work:

S.No.	Biological Activity	Parameters Used
1	Antimicrobial Activity	Molar Refractivity (MR), Hydrophobicity Parameter (π), Hammet's Electronic Parameter (σ), Resonance Parameter (R), Taft's Steric Factor (Es), B1, B5,L, $E_{HOMO,}$ E_{LUMO}

7. EXPECTED OUTCOMES:

- The pursuit of potent antimicrobial Chalcone derivatives drives innovation in drug discovery and development.
- Antimicrobial agents designed with greater specificity can lead to fewer side effects and lesser disruption to the body's natural microbial balance.
- CADD helps to focus on the most promising compounds so that they can minimize the synthetic and biological testing efforts.
- By employing computational techniques, the current study will enable the creation of superior chemicals which will exhibit stronger anti-microbial activity.
- The present study will forecast potential Chalcone compounds that could enhance anti-microbial action in addition to describing the molecular foundation of therapeutic activity.

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CHAPTER OUTLINE

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Chapter 2 Review of Literature
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